REMARKS

Applicants respectfully request reconsideration of this application, and reconsideration of the Office Action dated September 9, 2003 (Paper No. 23). Upon entry of this Amendment, claims 1-7, 9-11 and 21-24 will remain pending in this application. Claim 1 has been amended by incorporating into claim 1 the features of previous claim 8, which has been canceled. In addition, claims 11 and 23 have been amended to correct minor informal matters. Previously withdrawn claims 12-20 have also been canceled by this Amendment. No new matter is incorporated by this Amendment.

Applicants note the Examiner's suggestion to amend claim 11 by replacing the word "it" with --reagent-- and have amended claim 11 as suggested.

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Claims 1-11 and 21-24 are rejected under 35 U.S.C. § 103(a) as being obvious based on Norrgren et al. and Chen et al. in view of Wilbur et al. Applicants again respectfully traverse this rejection.

As an initial matter, Applicants provide the following background information. The present invention aims to address the problems associated with attaching a toxic binding moiety to the surface of a device. In all extracorporeal devices it is important that the immobilized toxic binding moiety remains stable during storage prior to treatment and during treatment. Furthermore, it is known that saturation of avidin with biotin or biotin derivatives will enhance the stability of the avidin molecule itself with respect to denaturing conditions. The present invention improves such stability by the use of a novel two-point attachment.

All developers of extracorporeal devices are faced with the problem of optimizing: a) clearance rate; b) sufficient accessible surface area to gain sufficient binding capacity, and c) biocompatibility. The latter is particularly important for devices intended for the processing of whole blood. Moreover, the extracorporeal device should be constructed in

such a way as to minimize the adsorption of endogenous components which are not desired to be cleared from the blood. By using the right length of the soluble linker, as taught in the present invention, the two biotin groups will bind to adjacent binding sites (of avidin subunits) on the same (strept)avidin molecule, thereby avoiding any intermolecular cross-linking of different avidin tetramers, which would alter the physical properties of the solid support. This is important, in particular, in the processing of whole blood, where uncontrolled alterations of the physical properties of the solid support through cross-linking could have a severe effect on the biocompatibility and binding accessibility of such a device.

The present specification discloses how the physical properties of the original avidin-coated device can be retained by avoiding inter-molecular interactions and minimizing any cross-linking, and at the same time minimizing the adsorption of endogenous biotin by blocking accessible binding sites for biotin.

It is known that saturation of avidin with biotin or biotin derivatives will enhance the stability of the avidin molecule with respect to denaturing conditions, such as elevated temperature, which normally occur during steam sterilization or irradiation. Yet Applicants surprisingly found that the two-point attachment minimizes the non-occupied biotin sites and therefore increase the stability of the device.

Applicants now turn to the claimed method. Independent claim 1 (from which the remaining claims all ultimately depend) concerns a method for the conditioning of an extracorporeal device for the extraction of toxic material from mammalian body fluids in connection with diagnosis or treatment of a mammalian condition or disease. The method includes treating the device having biotin binding ability with a solution comprising a reagent as defined in claim 1, which constitute a toxin binding moiety and a biotin dimer.

The presently claimed method enables the production of a novel toxic material binding device. The toxic material binding device may be used to remove undesirable

compounds from a fluid without removing essential endogenous components such as biotin from the body fluid. The above mentioned properties of the toxic material binding device, obtained by the invented method makes, for example, an avidin coated device ideal as a technology platform for the production of specific extracorporeal devices carrying various types of "toxin binding moieties." These tailor-made devices can be used for clearance of toxic compounds other than biotinylated components. The invention also enables the use of a well-characterized basic device which could in a single step be converted to a variety of different forms, each of them tailor-made for a specific extracorporeal treatment for clearance of endogenous or exogenous toxic compounds from the human blood circulation. By applying the methods of the present invention, such a "conditioning step" would be achieved without the addition of any organic solvent, or other chemicals, and could occur by recirculation at ambient temperature, either at an ordinary manufacturing facility or at the hospital site by the use of a block monitor used for treatment with, for example, Mitradep®, prior to treatment. It is clear that such a procedure will have significant implications on the cost of such devices and the time to market. The associated regulatory aspect would also be simplified in that the invention will most likely be classified as an "accessory to a device" and would thus not require an entirely new registration of the technology platform.

In the Office Action, it was asserted that anyone skilled in the art would be motivated to combine Norrgren and Chen with Wilbur. It is further asserted that "Wilbur et al, teach" the instant trifunctional linking compound as useful for absorbing to a column for extracting various compounds (see page 2, line 1-2). With all due respect, Applicants respectfully disagree with this conclusion. Applicant submit that Wilbur does not include such a teaching. The lines referred to in the Office Action state that "Purification techniques such as affinity chromatography frequently employ biotinylated materials". This is a part of a general description under "background of the invention" how "avidin

and streptavidin renders biotin compound useful for numerous applications" and does not imply that the biotin compounds described in the following text would in any way be more suitable or at all suitable for such application. Moreover, it does not disclose whether the biotin compounds should be a part of the chromatography device or used for separating biotinylated material from non-biotinylated material. In addition to that, affinity chromatography is a method of adsorbing components from a mixture of other components, followed by desorption of the desired components from the affinity device.

This is the only reference within Wilbur to anything even remotely related to the present invention. Extracorporeal techniques are faced with completely different problems compared to affinity chromatography described by Wilbur. For example, in an extracorporeal technique, the artisan is faced with the problem of being able to permit a body fluid to pass through the device without harming or changing the structure of essential components within the body fluid and, at the same time, allowing the toxic compound to be bound to the toxic binding moiety. Hence, such application requires features different from that of an affinity chromatography.

Applicants particularly note that Wilbur gives no guidance whatsoever to any of the biotin derivatives being immobilized to a surface or even used in any context where other compounds are immobilized or attached to a surface, regardless of the type of surface. In addition, in the Office Action, it is asserted that "trifunctional linkers are old and well known in combination with various specific therapeutic functional moieties" with reference to page 20, paragraph 2. However, page 20 paragraph 2, only mentions that biotinylated regents and biotin-containing compounds may be linked to targeting moieties. Page 20, paragraph 2 of Wilbur makes no mention about trifunctional or the number of biotin moieties. The only place within the teachings of Wilbur "tri-" is mentioned is in connection with the trimer on page 29, line 23. Specifically, trimeric biotin compounds are described which may be utilized for cross-linking of biotin-binding proteins (i.e.,

compounds comprising at least three biotin moieties) and these compounds may be used to create large complexes *in vivo* to amplify the therapeutic response, not to clear the body from surplus toxic material. In the present invention, a toxic material binding device which cross-linked biotin-binding proteins would, on the contrary, would not be useful in the present method.

The Office Action states that Wilbur teaches that a distance between each biotin moiety in a biotin trimer (i.e., consisting of three biotin (see compounds 46-48)) is preferably from about 20 to about 50Å. However, nothing in Wilbur teaches a person faced with the problem of attaching a toxic binding moiety to a surface in the direction of binding the toxic binding moiety to a biotin dimer, to pass a solution (comprising the biotin dimmer linked to a toxic binding moiety) through the device and obtain a toxic material binding device. Moreover, Applicants submit that nothing in Wilbur teaches or fairly suggests obtaining a toxic material binding device having the toxic binding moiety through the biotin dimer attached to the surface of the device.

Even though a trimer is mentioned, it does not automatically mean that it may successfully be used in a method to attach the trimer, wherein one part of the trimer is a toxic binding moiety to a surface, wherein the surface is located in an extracorporeal device.

In addition, Wilbur teaches that biotin multimers having more than three biotin moieties are useful for blood clearance of biotin binding proteins (see page 35, lines 1-2). However, Wilbur actually teaches away from the claimed invention in that Wilbur teaches away from using less than four biotin moieties in a method to produce a device. Thus, even when combined with the teachings of Norrgren and Chen, nothing in the combined teachings of the cited documents teach using the tri-functional moiety as recited in claim 1 in a method to clear away toxic components, and in particular, biotin binding molecules, from a body fluid.

Norrgren and Chen disclose a method to remove biotinylated antibodies from plasma by passing the plasma through an extracorporeal circuit which removes biotinylated antibodies that have not been bound within the body. Applicants submit the teachings of Norrgren are limited to the use of an avidin coated extracorporeal device for the removal of biotinylated therapeutic and diagnostic antibodies (i.e., an avidin binding device which removes from blood antibodies to which biotin and a radionuclide is linked).

Figure 1 of Norrgren, illustrates the general concept and the general setting for extra-corporeal treatment of a rat. In contrast, Applicants' invention discloses a special method featuring a (strept)avidin binding device. Norrgren does not disclose such properties, neither does Norrgren in any way describe the need or desire for a device with such properties. Furthermore, the more general application of the presently claimed method (i.e., the clearance of toxic components by and large and which does not contain biotin moieties) is outside the scope of the Norrgren, which deals with the clearance of biotinylated components.

Applicants submit the combined teachings of Norrgren, Chen, and Wilbur would not teach a person of ordinary skill in the art the claimed method which produces an extracorporeal device that has a biotin dimer attached to the surface linked to a toxic binding moiety which can remove different toxic compounds from a body fluid (such as blood) without binding endogenous components. This is because Wilbur teaches that biotin multimers having more than three biotin moieties are useful for blood clearance of biotin binding proteins (see page 35, lines 1-2), while Norrgren does not mention anything about the number of biotin moieties. Thus, the cited documents teach a person skilled in the art away from trying to use a biotin dimer linked to a toxic compound in a method to produce a toxic material binding device which can be used to remove a toxic compound from a body fluid.

In addition, Applicants' method gives rise to a device which has improved properties, such as increased stability of the immobilized proteins, retained physical properties and minimized absorption of endogenous components to the device. These are problems which people working within the area of affinity chromatography are not faced with. Accordingly, nothing in Wilbur, Chen, or Norrgren, teaches a person of ordinary skilled in the art to use a biotin dimer linked to a toxic compound in a method to obtain a device having the above-mentioned improved characteristics. Norrgren and Chen (which uses an extracorporeal device) do not even mention these effects as drawbacks which need to be improved, simply because most of these features are not relevant to the applications disclosed in the three documents. It is notable that an avidin coated device can, per se, only be used to remove either exogenous biotinylated substances or endogenous biotin.

The combination of, e.g., an avidin coated device with a biotin dimer and a toxic binding moiety constituting a strept(avidin) moiety permits the avidin coated device to be used as a platform technology, both for the removal of non-toxic targeting agents, and, after a single step conditioning procedure, as a device for the removal of the toxic material. Various applications of the two forms of an avidin-coated device in multi-step pretargeting are revealed in examples 5 and 6. As for the above embodiment, such "conditioning" will occur without organic solvent or other chemicals and would be performed by re-circulation at ambient temperature, either at an ordinary manufacturing facility or at the hospital site by the use of a blood monitor, either manually or pre-programmed, prior to treatment.

Applicants submit that one of ordinary skill in the art, having access only to the cited documents, would not have been motivated to arrive at the present invention. This is because Wilbur does not give any guidance to the use of extracorporeal techniques or even attaching those novel biotin oligomers to a surface, neither does it reveal any information which could be helpful in solving the problem of the present invention with respect to designing and applying these novel structures for the clearance of blood. If anything,

Wilbur teaches away from using biotin trimers in the therapeutic applications disclosed. Likewise, Norrgren and Chen do not give any guidance for a method which results in a device intended to clear the blood from toxin components other than biotinylated antibodies, which is outside the scope of the present invention. None of these documents discuss the problems faced in designing a device disclosed in the present invention which led to the present invention.

In summary, a person skilled in the art having access to the above-cited references and aiming to solve the problem behind the present invention would not have any incentive to combine any of the references as discussed above and arrive at the present invention as defined by the present claims. Accordingly, Applicants submit that this rejection is overcome and respectfully request that the rejection be reconsidered and withdrawn.

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Applicants respectfully submit that this Amendment and the above remarks obviate the outstanding rejection in this case, thereby placing the application in condition for immediate allowance. Allowance of this application is earnestly solicited.

Furthermore, if the Examiner deems that this Amendment does not place the application in condition for allowance, the Examiner is respectfully requested to contact Applicants' undersigned representative to discuss any remaining issues.

If any fees are due in connection with the filing of this Amendment, such as fees under 37 CFR §§1.16 or 1.17, please charge the fees to Deposit Account 02-4300; Order No. 033700.004.

Respectfully submitted,

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